Unraveling disease mechanisms in genetic white matter disorders

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Research question and background

Genetic white matter disorders (WMDs) are inherited encephalopathies selectively involving the white matter of the brain. Most are progressive, many are fatal and very few can be cured. Deeper insight in the pathophysiology of WMDs is essential to find openings for better treatment and, if possible, cure.

Two of the most prevalent genetic WMDs in the Netherlands are vanishing white matter (VWM) and the disorders of brain ion-and-water homeostasis, including *CLCN2*-related leukoencephalopathy. Although their disease mechanisms are still poorly understood, current evidence suggests that white matter astrocytes play a central role in the pathophysiology of both disorders.

Methods and tissues used

Availability of human brain tissue, including control tissue, is conditional for the successful identification of the disease mechanisms underlying genetic WMDs. Brain tissue of non-neurological controls without confounding neuropathology and neurological controls with multiple sclerosis obtained from the Netherlands Brain Bank was compared to genetic WMDs patients' tissue to investigate the pathogenetic role of white matter astrocytes in influencing the composition of the extracellular matrix in VWM and assess the expression of the astrocytic proteins involved in brain ion-and-water homeostasis. Methods included fluorescence immunohistochemistry and immuno-electron microscopy.

Results and conclusion

Neuropathology of VWM shows lack of myelin, tissue cavitation, no glial scarring and increased numbers of oligodendrocyte progenitors. We found that, compared to normal control and multiple sclerosis tissue, VWM white matter astrocytes are inhibited from maturation and retain the phenotype of astrocyte precursor cells. In line with astrocytes being immature, the white matter extracellular matrix is profoundly altered with overabundance of a high molecular weight form of the glycosaminoglycan hyaluronan. Hyaluronan is known to inhibit oligodendrocyte progenitor maturation, and could mediate other aspects of VWM neuropathology.[1]

The disorders of brain ion-and-water homeostasis are characterized by intramyelinic oedema in the white matter leading to tissue microvacuolation. Amongst these, *CLCN2*-related leukoencephalopathy is a novel disorder featuring MRI signal changes with restricted diffusion in the brain central white matter structures. We employed normal control white matter tissue to assess the cellular and regional expression pattern of the main proteins involved in ion-and-water homeostasis, including ClC-2, MLC1 and GlialCAM. We found that these proteins are expressed by astrocytes and enriched at the blood-brain and cerebrospinal fluid-brain barriers. ClC-2, in particular, shows enhanced membrane expression around blood vessels, in the glia limitans, ependymal lining, and astrocyte–astrocyte contacts in the white matter, strongly supporting a role in the panglial syncytium.[2]

Our findings support the presupposition that white matter astrocytes play a central role in the pathophysiology of VWM and provide new insights into the general mechanisms

underlying failure of white matter repair and disturbances in brain ion-and-water homeostasis.

References

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